

WORKING PAPER

Approaches to Intellectual Property and Innovation that Meet the Public Health Challenge of AIDS

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Part I. Introduction

In the global struggle against the AIDS epidemic, innovations in health technologies have played a central role. Since the mid-1990s, the availability of antiretroviral (ARV) therapy as an effective treatment has transformed HIV infection from a death sentence into a chronic, but largely manageable, disease. The global effort to make available ARV therapy in developing countries has seen a nearly 22-fold increase in ARV access over the 10-year period from 2001 to 2010, reaching 6.6 million people living with HIV.²

Against these achievements, however, the way forward towards achieving the target of putting 15 million people on ARV treatment by 2015, agreed to at the recent UN General Assembly High Level Meeting on AIDS,³ will not be any less challenging. The burden of AIDS still falls disproportionately on people in the developing world. Of the 33.3 million people living with HIV in the world today, over 80% reside in low- and middle-income countries. Sub-Saharan Africa bears an inordinate burden with two-thirds (22.5 million) of the world's people living with HIV/AIDS.⁴ The challenge remains to ensure affordable access to treatment for all those who need it.

Although a dual market for AIDS medicines made it possible for the early ARV therapies to be differentially priced for developing countries, it was, in fact, the introduction of generic ARVs that resulted in meaningful price reductions. In 2001, the Indian manufacturer, Cipla Ltd., offered its generic equivalent of the triple ARV combination (of 3TC+NVP+d4T), which reduced treatment costs from the originator price of \$10,000-15,000 to \$350 per patient per year.⁵ It is a process that continues today; first-generation generic ARVs in the market continue to exert a downward pressure on prices,

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2 UNAIDS. AIDS at 30: Nations at the Crossroads, 2011. Available from: <http://www.unaids.org/en/resources/unaidspublications/2011/>

3 UN General Assembly. Political Declaration on HIV and AIDS: Intensifying Our Efforts to Eliminate HIV and AIDS, UN General Assembly High Level Meeting on AIDS, June 2011. Available from: <http://www.ip-watch.org/weblog/wp-content/uploads/2011/06/2011-Political-Declaration-on-HIV-and-AIDS.pdf>

4 Global Report: UNAIDS Report on the Global AIDS epidemic 2010. Available from: http://www.unaids.org/globalreport/Global_report.htm

5 McNeil, Donald G. Indian Company Offers to Supply AIDS Drugs at Low Cost in Africa. New York Times, February 7, 2001. Available from: <http://www.nytimes.com/2001/02/07/world/indian-company-offers-to-supply-aids-drugs-at-low-cost-in-africa.html?pagewanted=3&src=pm>

which are now less than 1% of the originator prices in 2001.⁶ The valuable lesson learnt here is that had generic ARVs not been available, it would not have been possible to provide treatment for the millions who are alive today in the developing world.

A pressing concern today, after over a decade of efforts to expand ARV access, is the availability and the affordability of the next phase of ARV therapy. The transformation of HIV into a chronic disease requiring lifelong treatment has also brought with it the need for new and better treatments, including medicines that have fewer adverse effects and combinations or formulations that facilitate adherence, as well as those to overcome drug resistance. It is estimated that over 95% of people on treatment are now on first-generation ARVs.⁷ As drug resistance increases over time however, so too will the need for second- and third-generation medicines. Second-line ARV therapy will rely mostly on regimens comprising patented drugs. Generic manufacturers, notably in India, had previously been able to engage in the process of reverse engineering to produce copies of the originator first-generation ARVs, due to the absence of product patent protection in the country. The expiry of transition periods under the WTO TRIPS Agreement – in 2000, for developing countries to comply with the TRIPS Agreement and 2005, for countries that had not previously provided patent protection for pharmaceutical products – now limit the generic production of patented drugs and thus, affordable ARV access.

1.1 Scope and organization of paper

This paper examines the evolving relationship between IPR protection and pharmaceutical innovation, within the context of facilitating timely access to HIV treatment in developing countries.

The expiry of transition periods for the full implementation of the WTO TRIPS Agreement in developing countries is rapidly closing the windows of opportunity that permitted generic competition and follow-on innovations to adapt existing ARVs for resource-limited settings – key factors that have hitherto facilitated the scale up of ARV access in developing countries. Part II considers the twin challenges that now arise – how to ensure innovation and access to these future health technologies. With regard to upstream innovation, the question is whether and how IP protection will impede or facilitate discovery of new treatments or adaptation of existing ones. For downstream access, the primary concern relates to the potential for reduced, or absent, generic competition and the consequences for pricing and distribution of ARVs.

There is growing recognition that meeting the needs of those living with HIV, particularly in the developing countries, will likely require alternative approaches that improve upon the present patent-driven system of pharmaceutical innovation. In this regard, the paper examines two policy dimensions – the creation of an enabling environment and the use of innovative financing mechanisms – that can serve as strategic levers to enhance sharing of knowledge for R&D and innovation, and to ensure greater affordability of the fruits of such research.

Part III looks at two principal approaches by which to create an enabling IP environment – tiering and pooling. While these approaches have often been used strategically on the demand side to facilitate downstream access, they also have potential for enabling innovation further upstream in the R&D pipeline. In considering the Medicines Patent Pool and GlaxoSmithKline's patent pool, the paper draws out issues at the centre of debate. Where these are adequately addressed, this paper suggests that tiering and pooling arrangements, whether used separately or as complements, can open the door towards greater sharing of the building blocks of knowledge and thus to innovations otherwise not possible nor affordable.

Part IV examines the role of financing mechanisms – push and pull mechanisms – with the aim of assessing their effectiveness in re-engineering the value chain of R&D and innovation, and influence downstream access. The discussion on push mechanisms addresses two related aspects; up-front funding that diminishes the risk of investing in R&D and options for the public sector's strategic use of IPR licensing to ensure follow-on innovation and access. On pull mechanisms, Part IV examines recent prize proposals that have garnered significant attention, namely the Advance Market Commitments and Health Impact Fund, and highlights a number of considerations that should inform the structuring of prizes.

Finally, the paper suggests that a hybrid approach to financing innovation for access may yet offer the most potential, building on the strengths while lessening the shortcomings of the various mechanisms. The evident challenge is to determine the right combination of push and pull approaches, which balance the need to ensure sufficient financial incentive for innovation with the need to do at an affordable cost. The flow of public and philanthropic funds towards the global response to AIDS necessitates a careful examination of how fair returns from the public investment in R&D

6 UNITAID. Patent Pool Initiative: Implementation Plan, November 2009. Available from: http://www.medicinespatentpool.org/content/download/215/1231/version/1/file/ForWebsite_UNITAID_Patent_Pool_Implementation_Plan_-_Executive_Summary.pdf

7 AIDS at 30: Nations at the Crossroads. UNAIDS, 2011. Available from: <http://www.unaids.org/en/resources/unaidspublications/2011/>

may be ensured and the needs of those living with HIV can be adequately met. Drawing on a number of illustrative models, this paper proposes a metric for evaluating current and future proposals. While the obvious difficulty is that such an evaluation takes place in a context where many proposals have yet to be implemented, the aim is to provide policy makers a set of criteria and principles on which they can base their decisions.

Part II. Globalized intellectual property rights protection: implications for pharmaceutical innovation and access to medicines

Despite innovations in health technologies and new treatments for HIV, there is often a disparity between treatments available to those in developed countries and those in developing countries. The cost of treatments is clearly a factor limiting access. Through the lowering of ARV prices, largely through generic competition, the treatment of millions of people living with HIV has become possible over the past decade. The reality, however, is that most people in the developing countries may have access to only a handful of combinations of ARVs, with few or no alternatives, despite when side effects or treatment failure occurs, and that appropriate pediatric treatment still lags behind that for adults. Hence, there is a continuing need for affordable access to new and appropriate innovations in treatment.

In the context of the IPR regime put in place by the TRIPS Agreement, Part II considers the twin challenges that now arise – how to ensure innovation and access to future health technologies. An immediate priority is to ensure downstream access. In this context, the primary concern is the potential for reduced, or absent, generic competition and its effect on pricing and distribution. With regard to upstream innovation, the question is whether and how IPR protection will impede or facilitate discovery of new treatments or adaptation of existing ones.

2.1 A globalized IPR regime

The TRIPS Agreement has put in place a near-global IPR regime within the short span of 15 years. This represents a seismic shift from the pre-TRIPS environment wherein over 50 countries had not provided protection of pharmaceutical product patents.⁸ Although adopting a “minimum standards” approach, the TRIPS Agreement has, in fact, elevated the international standards of intellectual property protection by imposing standards of protection far stricter than those prevailing in developing countries at the time of its adoption. A significant number of developing and least-developed countries had also implemented the TRIPS requirements for patent protection on pharmaceutical products well before the expiry of the transition periods afforded them under TRIPS.⁹

The implementation of these higher IPR standards on a global scale raise a number of concerns: amongst them, whether the capacity for generic production would be impeded by patent restrictions in some countries, or that the availability of generic supply through importation would be hampered by patent restrictions in countries with manufacturing capacity.

At the height of the debate on patents on pharmaceuticals and access to medicines, a 2001 study suggested that the lack of patents on AIDS drugs in African countries meant that IPR protection could not constitute a significant obstacle to treatment access in and of itself.¹⁰ The experience of expanding ARV access in the developing countries has shown that access to affordable ARVs requires the interplay of different factors, such as capacity for generic production enabled by the absence of patent restrictions or the availability of generic supply through importation unimpeded by patent restrictions. In the case of many countries in Africa, the lack of patents did not translate into increased access. Absent generic availability at the time, high drug prices persisted across the continent of Africa, thus hampering access. Ghana's experience, in attempting to import generic ARVs, highlights another aspect of this interplay of factors. Glaxo challenged Ghana's import of Duovir, Cipla's generic version of its dual-ARV combination, Combivir, claiming infringement of four patents relating to Combivir. The challenge successfully removed Duovir from the market, although it was later determined by a team from Médecins Sans Frontières that three out of four patents claimed on Combivir were invalid, a determination supported by officials at the African Regional Intellectual Property Office (ARIPO), the regional patent organization to which Ghana is party. The fourth patent, related to a specific drug formulation of Combivir, did not apply to Duovir.^{11, 12}

The Ghana case highlights the need for access to accurate patent information – a need that will only increase as patent numbers rise – and the issue of the available capacity in developing and least-developed countries to effectively

8 UNCTAD. The TRIPS Agreement and Developing Countries, Geneva, 1996. Available from: http://www.unctad.org/en/docs/ite1_en.pdf

9 Thorpe, Phil. Study on the Implementation of the TRIPS Agreement by Developing Countries, Study Paper No. 7 for the UK Commission on Intellectual Property Rights, 2001. Available from: http://www.iprcommission.org/papers/pdfs/final_report/Ch7final.pdf

10 Attaran, Amir and Gillespie-White, Lee. Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa? 2001; 286(15): 1886-1892. doi:10.1001/jama.286.15.1886

11 Glaxo blocks importation of generic Combivir into Ghana. January 2001. Available from: <http://i-base.info/htb/4062>

12 Schoofs, Mark. Glaxo Attempts to Block Access to Generic AIDS Drugs in Ghana. , December 1, 2000.

administer and manage the IPR system. Many developing countries do not have electronic databases storing such patent data, hence the need to rely on manual searches for patent information, which can be inaccurate, incomplete and time-consuming. As noted in a recent WIPO study, the “availability of legal status data of some 50 countries (most of them developing countries and LDCs) is limited” because many of them do not have the legal status data in digital form and national on-line registers.¹³

Nor do many developing countries conduct substantive examination of patent applications; often patents are registered on demonstration that it has been granted by an established patent office such as the EPO or the USPTO. This raises obvious concerns, not least because of the lack of filter to check against abuses or a system to monitor for subsequent invalidation of the patents at the other patent offices. In relying on the substantive examination by developed country patent offices, developing countries are foregoing the ability to adopt TRIPS flexibilities, such as stricter patentability criteria for pharmaceutical inventions.

The expansion of ARV access in the developing world has also changed the economics of innovation and IPR. Increased funding support for the procurement of AIDS drugs, with the establishment of initiatives such as PEPFAR and Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), has enlarged the size of the public, as opposed to the private, market for AIDS drugs in developing countries. Where previously, there might have been little incentive to patent AIDS drugs in impoverished developing countries with little purchasing power or manufacturing capacity, donor funding for ARV procurement, coupled with the ease of registering patents, may provide drug companies a further incentive to seek patents.

India, as is well known by now, was one of the few countries to take advantage of the TRIPS transition provision that permitted delaying product patent protection until 2005. The earlier Indian patent regime, coupled with an enabling policy environment, facilitated the growth of the domestic pharmaceutical industry. Under these circumstances, Indian firms were able to shorten progressively the time lag between the introduction of a pharmaceutical product in the global market by the inventor and the marketing of the generic version in the Indian market.¹⁴ The possibility of production via alternative processes and reverse engineering enabled the generic production of ARVs and other drugs patented elsewhere. The introduction of the product patent regime post-2005 is, however, already having an effect in India. The new patent legislation also incorporated a number of safeguards – such as stricter patentability criteria for pharmaceutical inventions and a pre-grant opposition procedure. A number of important successes in the challenge of patent applications relating to key ARVs that do not meet the patentability criteria¹⁵, including recent rejections in 2011 by the Indian Patent Office of the patent applications related to two ARVs, atazanavir and lopinavir/ritonavir¹⁶, has allowed for the continued production of generic ARVs.¹⁷ Despite these safeguards and successes, however, the generic industry will likely face increasing constraints as options for generic production and supply of newer drugs become more limited.

Although the Doha Declaration on the TRIPS Agreement and Public Health re-affirmed the right of developing countries to exercise a range of flexibilities under the TRIPS Agreement, including the use of compulsory licensing to access affordable generic drugs, only a few developing countries have done so. The use of the mechanism to permit compulsory licensing to manufacture generic pharmaceutical products for export, under the WTO General Council Decision of 30 August 2003, has also been limited. Canada’s 2004 Access to Medicines Regime (CAMR) has been used only once, to authorize the production of a fixed-dose ARV combination for export to Rwanda in 2008.¹⁸ The CAMR regime has been criticized for imposing unnecessary restrictions, not required under TRIPS or the General Council Decision, which do not take account of the practical realities of drug procurement and which have hindered the effective supply of affordable generics to developing countries.¹⁹ The implementation of product patent protection under TRIPS has had the effect of restricting generic production, not only in India, but also in the other developing countries with manufacturing

13 WIPO. Feasibility Study on the Establishment of National Patent Register Databases and Linkage to Patent Scope, CDIP/4/3 REV./STUDY/INF/3, Geneva, 2011. Available from: http://www.wipo.int/edocs/mdocs/mdocs/en/cdip_4/cdip_4_3_rev_study_inf_3.pdf

14 UNCTAD. Transfer of Technology for Successful Integration into the Global Economy, UNCTAD/ITE/IPC/2003/6, New York and Geneva, 2003. Available from: http://www.unctad.org/en/docs/iteipc20036_en.pdf

15 Médecins sans Frontières. Untangling the Web of Antiretroviral Price Reductions, 2010. Available from: http://utw.msaccess.org/background/overcoming_challenges

16 Mukherjee, Rupali. “AIDS drug patents by Abbott, BMS rejected”, Times of India, 13 January 2011, available from: http://articles.timesofindia.indiatimes.com/2011-01-13/india-business/28379392_1_Leena-menghaney-ritonavir-patent-applications

17 Submission made by Sangeeta Sashikant, Third World Network, Malaysia for the Asia Pacific Regional Dialogue of the Global Commission on HIV and the Law.

18 WTO. Minutes of Meeting, Council for Trade-Related Aspects of Intellectual Property Rights, 1 June 2010, IP/C/M/62, available from: <http://docsonline.wto.org/>

19 Submission made by Patricia Allard, Canadian HIV/AIDS Legal Network, Canada for the High Income Countries Dialogue of the Global Commission on HIV and the Law.

capacity like Brazil, China and Thailand.²⁰ Restrictions on generic production in India will have significant impact on access to ARVs worldwide, given the prominence of Indian generic manufacturers in the supply of ARVs to developing countries. A review of transactional data from the Global Fund, UNITAID and WHO shows that Indian-produced generic ARVs accounted for more than 80% of the donor-funded developing country market, by value, since 2006 and in 2008, comprised 87% of ARV purchase volumes.²¹

2.2 Access: Prices and patents

To date, ARVs have remained the mainstay of treatment for HIV. A critical component of the global AIDS response has thus been the expansion of access to ARV therapy. Treatment and care comprise the largest expenditure in relation to the other components of the overall AIDS response in low- and middle-income countries. The financing needs for treatment are set to rise – from US\$7.4 billion in 2009 to US\$19.3 billion in 2015²² – but the recent financial crisis and a reduction in donor contributions have raised concerns of an even larger funding gap. Given that many countries in the developing world still depend on international assistance for their treatment and care programmes, reducing the costs of ARVs and other HIV treatments is a key priority to render scale-up of ARV access financially sustainable for donors and eventually, national governments.

Ensuring affordability of ARVs becomes even more significant in the face of results from recent clinical trials, which demonstrate the effectiveness of ARV therapy as prevention. The iPrEx study showed that pre-exposure prophylaxis (PrEP) in the form of a daily dose of an oral ARV taken by HIV-negative, gay and bisexual men and transgender women, reduced the risk of acquiring HIV infection by 43.8%.²³ More recently, the HPTN 052 clinical trial showed that treatment of HIV-infected individuals with ARV therapy reduces the risk of sexual transmission of HIV to an uninfected partner by 96%.²⁴ The latest and largest study to date, the Partners PrEP Study, has also confirmed the effectiveness of ARVs as a HIV prevention strategy, showing that those who received tenofovir (TDF) had an average of 62% fewer HIV infections, while those receiving tenofovir combined with emtricitabine (FTC/TDF) had 73% fewer HIV infections, compared to those receiving the placebo. The Partners PrEP Study was conducted in nine research sites in Kenya and Uganda, involving 4,758 HIV serodiscordant couples, in which one partner has HIV and the other does not.²⁵

The capacity of India's domestic manufacturers for generic production, due to the lack of product patent protection, has already been described. Similarly, in Brazil, where universal access to HIV treatment is provided, a major factor contributing to the effective implementation of this policy was the capacity for local production of ARVs. Production of generic ARVs began in the early 1990s, as the domestic intellectual property legislation in force at the time did not include patent protection for pharmaceutical products and processes.²⁶ Scaling up generic production of HIV treatment offers the prospect that economies of scale and thereby lower prices for active pharmaceutical ingredients might be realized.

Generic production of newer drugs was, however, constrained when Brazil adopted its Industrial Property Law (Federal Law 9279/96), which sought to implement the provisions of the TRIPS Agreement. Coming into force in 1997, the Brazilian legislation adopted the TRIPS obligations well before the deadline for developing countries, including the 2005 deadline for those countries that had not previously provided pharmaceutical patents. One implication of the new legislation was the increased cost of ARV procurement as the need for newer, patented medicines arose, raising concerns for the sustainability of the national treatment programme. In 2005, data from the General Coordination of Pharmaceutical Assistance to Strategic Medication of the Ministry of Health indicated that a third of the budget was spent on domestically-produced drugs, while two-thirds was spent on imported patented drugs.²⁷ In 2007 it was

20 Brazilian Interdisciplinary AIDS Association – ABIA. Intellectual Property Rights and Access to Medicines: Civil Society Resistance in the Global South, 2009.

21 Waning, Brenda, Diedrichsen, Ellen, Moon, Suerie (2010). A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries 2010, 13:35 Available from: <http://www.jiasociety.org/content/13/1/35>

22 UNITAID. Patent Pool Initiative: Implementation Plan, November 2009. Available from: http://www.medicinespatentpool.org/content/download/215/1231/version/1/file/ForWebsite_UNITAID_Patent_Pool_Implementation_Plan_-_Executive_Summary.pdf

23 Crowley, Jeffrey. NIH-Funded Study Finds Daily Dose of Antiretroviral Drug Reduces Risk of HIV, Office of National AIDS Policy, 2011. Available from: <http://www.whitehouse.gov/blog/2010/11/23/nih-funded-study-finds-daily-dose-antiretroviral-drug-reduces-risk-hiv>

24 HIV Prevention Trials Network, Press Release, dated 12 May 2011. Available from: http://www.hptn.org/web%20documents/PressReleases/HPTN_052PressReleaseFINAL5_12_118am.pdf

25 University of Washington International Clinical Research Center. Pivotal study finds that HIV medications are highly effective as prophylaxis against HIV infection in men and women in Africa, Press Release, embargoed until 13 July 2011. Available from: http://www.hanc.info/Documents/PrEP_PressRelease-UW_13Jul2011.pdf

26 Brazilian Interdisciplinary AIDS Association – ABIA. Intellectual Property Rights and Access to Medicines: Civil Society Resistance in the Global South, 2009.

27 Reis, Renata, Vieira, Marcela Facaca and Chaves, Gabriela. Access to Medicines and Intellectual Property in Brazil: A Civil Society Experience, in *Intellectual Property Rights and Access to ARV Medicines: Civil Society Resistance in the Global South*, 2009, Brazilian Interdisciplinary AIDS Association – ABIA. Available from: http://www.abiaids.org.br/_img/media/Intellectual_Property_internet.pdf

estimated that 80% of the budget was used to procure 11 patented medicines, while 20% was spent on 7 locally-produced medicines.²⁸

As the need for second- and now third-line regimens arises, it will be important to consider all available measures to reduce prices and increase treatment access. In low-income countries, the annual price per person will increase from US\$136 to US\$243 for first-line regimens to US\$572 to US\$803 for second-line regimens. In the lower-middle income countries, the price differentials would range from US\$116 to US\$667 for the first-line, compared to US\$818 to US\$1545 for the second-line regimens. The difference becomes even wider in the upper-middle-income countries, where first-line regimens range from US\$161 to US\$1033 and second-line regimens range from US\$3393 to US\$3647.²⁹

This raises concern in the context of new treatment needs. High prices have the potential to affect the speed of treatment introduction as well as the choice of treatment options. Although prices for first-line ARVs have declined by orders of magnitude over the past 15 years, prices still loom high compared to domestic purchasing power in developing countries. WHO's recent recommendation to substitute stavudine with the less toxic tenofovir or zidovudine in first-line ARV regimens clearly demonstrates this concern because the first-line regimens that include tenofovir cost up to three times more than stavudine-based regimens.³⁰ Prices can affect procurement patterns, with low-income countries choosing not to purchase higher priced ARVs. A survey of the Global Fund's ARV transaction data showed that low-income countries procured nearly eight times the quantity of nevirapine compared to efavirenz, while lower middle-income countries bought almost 2.5 times the quantity of efavirenz over nevirapine.³¹ Although a number of reasons might explain this difference, the higher price of efavirenz is certainly one factor. In the Commonwealth of Independent States (CIS) countries, where it appeared that pharmaceutical companies were strategically pricing their products at rates more suitable to the markets of Western Europe, the higher prices had the effect of slowing the introduction of ARV therapy in these countries.^{32 33}

Market exclusivity over one drug may also affect the pricing and access to other drugs. The case of ritonavir (Norvir), a protease inhibitor from Abbott, is illustrative. Patented and initially marketed as a standalone component drug in a triple ARV regime, ritonavir was later found to enhance the effectiveness of other protease inhibitors, making it sought after as a "booster" for other protease inhibitors. Abbott marketed its own ritonavir-boosted combination with lopinavir (Kaletra). But when other ritonavir-boosted combinations from competitors, GlaxoSmithKline and Bristol Myers Squibb, entered the market, Abbott instituted a 400% increase in the wholesale price of ritonavir overnight, while keeping the price of Kaletra the same. The suit against Abbott alleged that the "re-pricing" of ritonavir violated U.S. antitrust laws because Abbott exploited its monopoly position as the sole manufacturer of ritonavir in order to protect another Abbott drug, Kaletra, from competition against other combinations requiring ritonavir as a booster. Although the returned verdict did not support the antitrust claim, Abbott was found to be in breach of the contract struck with competitors for the supply of ritonavir.³⁴ Protease inhibitors are important components of WHO-recommended second-line ARV regimens. If it were not for the availability of therapeutic alternatives, given that ritonavir is currently the only approved booster in existence, prices of second-line ARV regimens would likely be less accessible.

2.3 Innovations for developing country needs

Another important factor in treatment access is the suitability of the treatments for the specific needs of populations in developing countries. Since originator companies develop ARVs primarily for the developed country markets, the particular needs of developing country populations may not be taken into account in the drug development process, and the modifications or improvements needed to address those needs may not be a priority. These adaptations include heat-stable formulations to enable easy transportation or fixed-dose combinations to increase adherence.

The WHO's ARV treatment guidelines, originally published in 2002 and currently in its 2010 revision, are intended to

28 Reis, Renata, Vieira, Marcela Facaca and Chaves, Gabriela. Access to medicines and intellectual property in Brazil: reflections and strategies of civil society, *Sur - International Journal on Human Rights*, No. 8, June, 2008. Available from: http://www.surjournal.org/eng/conteudos/getArtigo8.php?artigo=8,artigo_chaves.htm

29 UNDP-UNAIDS-WHO. Using TRIPS Flexibilities to improve access to HIV treatment, Policy Brief, 2010. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/policy/2011/JC2049_PolicyBrief_TRIPS_en.pdf

30 UNDP-UNAIDS-WHO. Using TRIPS Flexibilities to improve access to HIV treatment, Policy Brief, 2010. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/policy/2011/JC2049_PolicyBrief_TRIPS_en.pdf

31 Vasan, Ashwin, Hoos, David, Mukherjee, Joia S, Farmer, Paul E, Rosenfield, Allan G, and Perriens, Joseph H. The pricing and procurement of antiretroviral drugs: an observational study of data from the Global Fund. *Bulletin of the World Health Organization* 2006; 84: 393-398.

32 World Health Organization. Action needed to lower prices of antiretroviral treatment in Commonwealth of Independent States region (summary of recommendations of the meeting of the Coordination Council on HIV-infection problems of the CIS Member-States). Baku, Azerbaijan; 24-25 February 2005. Available from: <http://www.who.int/3by5/mediacentre/news42/en>

33 Vasan, Ashwin, Hoos, David, Mukherjee, Joia S, Farmer, Paul E, Rosenfield, Allan G, and Perriens, Joseph H. The pricing and procurement of antiretroviral drugs: an observational study of data from the Global Fund. *Bulletin of the World Health Organization* 2006; 84: 393-398.

34 For further details, see for e.g., <http://keionline.org/prices/ritonavir> and <http://www.lieffcabraser.com/antitrust/case/431/norvir>

provide evidence-based recommendations outlining a public health approach to the delivery of ARV therapy, taking into account developing country settings with limited health systems capacity and resources. The 2003 ARV treatment guidelines, regarded as the cornerstone of the WHO “3 by 5” campaign to scale up ARV access, encouraged the use of ARVs in fixed-dose combinations (FDCs) as a means to promote treatment adherence and limit the emergence of drug resistance.³⁵ It was significant that the WHO prequalified three Indian generic manufacturers, which produced the fixed-dose ARV combinations in accordance with the WHO-recommended first-line treatment regimens. Since then, the WHO guidelines have continued to encourage use of FDCs. The 2010 guidelines, in combining the latest clinical evidence to prioritize the best treatment options with considerations of acceptability, cost and feasibility, continues to encourage use of FDCs, on account of their simplicity of use and low pill burden.³⁶

Indian generic manufacturers were able to combine the component ARVs into the WHO-recommended regimens because of the absence of product patents at the time. The only available triple-ARV FDC from the originator companies then was GSK’s Trizivir, which combined the 3 GSK-owned components of abacavir, AZT and 3TC. The problem was that the combination did not reflect the WHO-recommended regimens for ARV therapy. Cipla, Ltd. produced the first FDC combining the WHO-recommended first-line ARV regime, containing nevirapine, stavudine (d4T) and lamivudine (3TC). Patents related to each of the components were held by different parties – Yale (stavudine), BioPharma/Glaxo (lamivudine) and Boehringer Ingelheim (nevirapine) – but availability of the components as generic drugs in the developing world enabled the introduction of this FDC at a much lower price. The absence of intellectual property barriers has also resulted in the development of improved ARV formulations, such as pediatric dosage forms. By 2009, the United States Food and Drug Administration (FDA) and the WHO Prequalification Programme approved or pre-qualified 57 adult FDCs and 31 pediatric ARV tablets produced by Indian generic manufacturers, but only eight adult FDCs and 14 pediatric ARV tablets produced by non-Indian and originator manufacturers.³⁷

IPRs on HIV treatment shape the conditions for cross-licensing for generic use of drugs in fixed-dose combinations or new pediatric formulations. Such IPRs can also spell the difference between affordability or not in resource-limited settings. The absence of IPR restrictions will play an even greater role for second-line treatments for HIV/AIDS in the future.

2.4 The pipeline for HIV medicines, diagnostics and vaccines

In a globalized world, expectations of life-saving treatment may cross borders well before actual access takes place. The struggle for access to ARVs in developing countries is perhaps the quintessential example of this. The moral dimension of this problem is that a significant number of those living with HIV do not have the personal means, nor do they live in countries where the governments could afford access to life-prolonging treatment. In looking at the pipeline for new and more effective AIDS treatments, the challenge will be to narrow the gap in the mismatch between where the disease burden is greatest and where the innovation and development occur.

Over the last three years, significant advances in HIV treatments have led to new therapeutic classes being approved for use, along with new drugs from the older classes. The new drug classes have different mechanisms of action to target HIV, thus expanding the treatment options for people living with HIV. The 2010 pipeline report from Treatment Access Group (TAG), the U.S.-based organization tracking the R&D landscape for HIV treatment, notes that there are “(f)ive new compounds and combinations... in advanced phase III studies [the final stage of clinical testing of drugs before market approval] and expected to be filed for US FDA review in 2010–2011. Additional drugs in existing and new classes, the latter including maturation and attachment inhibitors, are in earlier phases of testing.”³⁸

The pipeline for future treatments is important because current treatments, albeit effective, are not perfect. The challenges for innovation in AIDS treatment are the development of new therapies to combat multi-drug resistant HIV, but in developing countries, the added challenge is to develop suitable combinations that increase adherence in resource-limited settings, including those that use more economical components, and pediatric formulations.³⁹ Heat-stable formulations of ARVs are also important innovations for developing country needs. The TAG 2010 pipeline report notes that development of a heat-stable formulation of ritonavir as a standalone drug took another five years, despite the same compound being already available and marketed as a heat-stable co-formulation with lopinavir (heat-

35 World Health Organization. Scaling up Antiretroviral Therapy in Resource Limited Settings: Treatment Guidelines for a Public Health Approach, 2003 Revision. http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf

36 World Health Organization. Antiretroviral Therapy for HIV Infection in Adults and Adolescence: Recommendations for a Public Health Approach, 2010 Revision. http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf

37 Waning, Brenda, Diedrichsen, Ellen, Moon, Suerie (2010). A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries *Journal of the International AIDS Society* 2010, 13:35 Available from: <http://www.jiasociety.org/content/13/1/35>

38 Treatment Action Group. TAG 2010 Pipeline Report. Available from: <http://www.treatmentactiongroup.org/publication.aspx?id=3798>

39 Treatment Action Group. TAG 2010 Pipeline Report. Available from: <http://www.treatmentactiongroup.org/publication.aspx?id=3798>

stable version of Kaletra). Médecins sans Frontières has accused Abbott of delaying the development to build market advantage for its own protease inhibitor and to restrict treatment choices, particularly in the developing world.⁴⁰

Yet another factor is the need to take account of limited capacity of health infrastructure in developing countries. Hence, treatment requiring complicated diagnostic testing would be impractical and unaffordable in developing country settings where often even simple laboratory monitoring is rarely available. The entry inhibitor, maraviroc, for example, which requires a complicated diagnostic test costing more than US\$ 1,900, would not in its current form be a viable treatment option in developing countries.⁴¹

Clinical trials designed for developed country populations will not provide data on use in the case of tuberculosis and malaria co-infections, which are prevalent in developing countries. There remains a lack of data on the drug interactions, such as that between antimalarials and ARVs, despite the fact that 80% of people living with HIV live in regions where malaria is endemic.⁴² There is also a dearth of safety and efficacy data for children, despite the system of incentives and obligations put in place by the U.S. FDA and the European Medicines Agency (EMA) to encourage submission of data for pediatric use. The FDA requires submission of pediatric data assessments from manufacturers when they seek marketing approval, although waivers can be obtained subject to documentation detailing why a pediatric version of the drug or biologic cannot be developed.⁴³ The FDA is also authorized to extend market exclusivity for 180 days as an incentive for the conduct of pediatric safety and efficacy studies. Similarly, the EMA also requires manufacturers to provide a pediatric investigational plan (or request a waiver) as part of their application.⁴⁴ This lack of data can be attributed in part to the difficulties of conducting clinical trials in children, while another key factor is the absence of a market in many developed countries where pediatric HIV has virtually been eliminated.

Aside from new treatments, there is a clear need for HIV diagnostic tools appropriate for developing country use. The current 2010 WHO ARV treatment guidelines notes that while laboratory monitoring should not be a barrier to initiating ARV therapy, it acknowledges that the newly recommended ARV regimens may require more laboratory monitoring than current regimens.⁴⁵ Hence, the use of viral load testing is recommended, where feasible, to improve the identification of treatment failure. Viral load testing is also essential to follow HIV-infected infants and to monitor virological suppression in pregnant women to reduce the risk of mother-to-child transmission. Monitoring of CD4 counts also can play an important role in monitoring for treatment response and resistance. Although it has been shown that scale up of ARV therapy to developing countries, based on CD4 cell counts through routine clinical and/or laboratory monitoring, can be successfully initiated, it does not negate the urgent need for a CD4 tool in countries where even routine clinical monitoring is scarce. The TAG 2010 pipeline report highlights the development of two diagnostic tools, designed as point-of-care tools to measure viral load and CD4 counts. Key factors influencing their usefulness in developing countries will certainly be ease of use and price.

It is obvious that a safe, effective and affordable AIDS vaccine is the best hope of ending AIDS, but the vaccine development process has been difficult. With most candidates still at Phase I or II, the 2009 efficacy trial in Thailand of two candidates, ALVAC and AIDSVAX, has offered the most hope.⁴⁶ The results of the Thai trial do not appear promising but the data arising from the trial may contribute to the next breakthrough. Given the scale of the difficulty of the venture, progress towards an AIDS vaccine will depend not only on continued scientific advances, but also availability of financial resources to maintain the forward momentum for R&D efforts.⁴⁷

Advances in treating AIDS must take account of the needs of people in developing countries where the preponderant number of those with HIV/AIDS lives. In this context, might developing country manufacturers be better placed than originator companies to do this? Although the traditional preoccupation of developing country generic manufacturers

40 Médecins sans Frontières. Approval of heat-stable ritonavir ends years of neglect by Abbott: Years of medical double standards and stranglehold by Abbott come to an end, 12 February 2010. Available from: <http://www.msaccess.org/main/access-patents/heat-stable-ritonavir-approved/>

41 Médecins sans Frontières. Untangling the Web of Antiretroviral Price Reductions, 14th Edition, 2011. Available from: [http://www.msaccess.org/resources/key-publications/key-publication-detail?tx_ttnews\[tt_news\]=1706&cHash=8a79a14f7f](http://www.msaccess.org/resources/key-publications/key-publication-detail?tx_ttnews[tt_news]=1706&cHash=8a79a14f7f)

42 Treatment Action Group. TAG 2010 Pipeline Report. Available from: <http://www.treatmentactiongroup.org/publication.aspx?id=3798>

43 Tabor, E. FDA requirements for clinical studies in pediatric patients. *Regulatory Focus* 14:16-21, 2009. Available from: <http://www.quintiles.com/elements/media/white-papers/fda-requirements-clinical-studies-pediatric-patients.pdf>

44 Regulation (EC) No 1901/2006 (Paediatric Regulation) amended by Regulation (EC) No 1902/2006. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580025b8b&jenabled=true

45 World Health Organization. Antiretroviral Therapy for HIV Infection in Adults and Adolescence: Recommendations for a Public Health Approach, 2010 Revision. Available from: http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf

46 Treatment Action Group. TAG 2010 Pipeline Report. Available from: <http://www.treatmentactiongroup.org/publication.aspx?id=3798>

47 International AIDS Vaccine Initiative (IAVI). R&D Models: Lessons from Vaccine History, Policy Research Working Paper #14, June 2007. Available from: http://www.iavi.org/Lists/IAVIPublications/attachments/6e919e15-fb88-4519-af13-d312aa3806cd/IAVI_RD_Models__Lessons_from_Vaccine_History_2007_ENG.pdf

has been the copying and manufacturing of existing products discovered and developed elsewhere, many firms in these markets over the past decade are increasingly adapting health technologies to developing world contexts, as has been the case with Indian generic manufacturers with FDCs of ARVs described above. Working in the developing country context, the manufacturers can also leverage process innovations and reduce labor costs to offer products at more affordable prices.⁴⁸

2.5 Future challenges for innovation and access

Data from the US FDA's Center for Drug Evaluation and Research (CDER) show that 21 new molecular entities (NMEs) were approved in 2010, which was well within the range of 18-26 NMEs approved in the past 5 years since 2006. This also appears to be the average number of NMEs approved for the past decade; approval data since 2001 indicates that the average NME approvals are in the range of 22.9 per year. The CDER has not seen an increase in NME applications. In fact, except for 2002, the 23 NME applications filed in 2010 is the lowest number in over 15 years.⁴⁹ Analysis of earlier drug approval data shows a similar trend. During the 12-year period between 1989-2000, only a third (35%) of the 1035 new drugs approved were products with new active ingredients or new molecular entities (NMEs), while the other 65% used active ingredients that were already available in a marketed product.⁵⁰

Pharmaceutical innovation has faltered though IP protections in the industry continue to mount. In its 2009 Pharmaceutical Sector Enquiry, the European Commission noted the industry's use of strategies aimed at extending the breadth and duration of its patent protection. These practices included the filing of numerous patent applications on the same drug to form "patent clusters" or "patent thickets" aimed at delaying generic market entry. An examination of the patent portfolios of blockbuster products indicated a steady rise in patent applications throughout the product life cycle, including after the product launch. Individual drugs could therefore be protected by up to 100 product-specific patent families, with as many as 1,300 patents across the European Union Member States.⁵¹

The concerns over IPR protection and its impact on innovation and access will likely grow in the near term. One factor is the continuing move towards increased levels of IPR protection under regional and bilateral free trade agreements (FTAs). These FTAs, negotiated outside of the WTO ambit, often include IPR provisions that go beyond the standards prescribed by TRIPS. Developed countries like the United States, the European Union, and Japan, which have enacted TRIPS-plus provisions within their own domestic legislation, such as patent term restoration laws to increase the patent term and data exclusivity, routinely require the same level of protection from developing country trading partners in their trade negotiations. Concluded US free trade agreements, such as the Central American Free Trade Agreement (CAFTA), the US-Singapore Free Trade Agreement and the US-Morocco Free Trade Agreement, have triggered concerns, in part, due to the TRIPS-plus provisions found within them. Although the UN agencies and other groups have cautioned about the implications of TRIPS-plus provisions on access to medicines⁵², ongoing negotiations, such as the EU-India and Trans-Pacific Partnership continue to put forth these terms.

As modern medicines shift towards more complex biologics, the greater complexity of biologics also promises greater challenges than the conventional small-molecule drugs. Already one out of four new medicines receiving U.S. FDA approval is a biologic.⁵³ Biologics are medicines produced from living cells and comprise vaccines as well as many of the cutting edge therapies emerging for treating cancer, multiple sclerosis, Alzheimer's disease, and rheumatoid arthritis. By 2014, it is anticipated that biologics will make up half of the total sales of the top 100 medicines on the U.S. market.⁵⁴

Although a number of patents pertaining to certain biological products will expire in the near future, the concern lies with the possibility that these patent expirations may not be accompanied by the introduction of competing, lower-cost biologics in the marketplace. The problem lies with moves to introduce data exclusivity protection for biologics, which would have the effect of holding off generic competition for periods much longer than conventional, small-molecule drugs despite the expiry of relevant patents related to the original biologic. The European Union has provided a 10-year post-regulatory approval data exclusivity protection for biologics. In the US, a similar measure has been introduced

48 Rezaie, Rahim & Singer, Peter A (2010). *Global health or global wealth?* Nature Biotechnology, Vol 28, No 9, September 2010

49 Comparison of NMEs approved in 2010 with previous years, US Food and Drug Administration. Available from: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM242695.pdf>

50 NIHCM (2002) Changing Patterns of Pharmaceutical Innovation. Available from: <http://nihcm.org/pdf/innovations.pdf>

51 European Commission. Pharmaceutical Sector Enquiry Final Report 2009. Available from: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_en.pdf

52 The Report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, Anand Grover, A/HRC/11/12, 31 March 2009. Available from: http://www2.ohchr.org/english/bodies/hrcouncil/docs/11session/A.HRC.11.12_en.pdf

53 Schacht, W.H., and Thomas, J.R. (2009). "Follow-On Biologics: Intellectual Property and Innovation Issues." Congressional Research Service RL33901. Available from: <http://opencrs.com/document/RL33901/2009-08-03/download/1013/>.

54 EvaluatePharma. (2009). World Preview 2014.

through the Biologics Price and Competition Act 2009. The Act, enacted as part of the healthcare reform in the country, provides an abbreviated regulatory pathway for follow-on biologics,⁵⁵ similar in concept to the approval of generic drugs. As part of the package however, a 12-year data exclusivity protection for biologics has been incorporated, raising concerns of greater delays for generic competition.

Part III. An enabling environment for innovation and access

Creating an enabling environment for innovation and access involves the strategic use of intellectual property rights and other incentive systems to advance public health. This opportunity, if not obligation, falls not just upon the socially responsible corporation, but also upon the public sector to deploy IPRs so as not to encumber, but to ensure needed innovation and affordable access to the health technologies that might combat AIDS. Two approaches—tiering and pooling—apply not just to innovation upstream in the R&D pipeline, but also to access downstream in the delivery system. Such arrangements may open the door to building blocks of knowledge otherwise not accessible and drug combinations not otherwise affordable.

3.1 Tiering

Launched in May 2000, the Accelerating Access Initiative – a partnership among WHO, UNAIDS, UNICEF, UNFPA, the World Bank and 7 research-based pharmaceutical firms – set out to make available lower prices for ARVs on a company-by-company, drug-by-drug, country-by-country basis.⁵⁶ Tiered pricing – the approach taken – commonly comes to mind as a strategy for enabling affordable access to those in resource-limited settings.

Under tiering arrangements, the market is segmented between those receiving preferential treatment and those not receiving such treatment. When tiering is over price, the segmentation of the market, in part, often reflects the disparity in market share value between industrialized and developing countries. Eighty percent of the value of global pharmaceutical sales traces to just nine OECD countries.⁵⁷ The existence of a dual market, where one segment can generate significantly greater returns than the other, may be critical for differential pricing to work for most multinational pharmaceutical firms. When there is leakage or arbitrage between those market segments, this differential erodes. Despite such concern, parallel trade in the European Union and the United States has been miniscule, accounting for only 2% of the EU market and 0.5% of the US market by value.⁵⁸

More commonly, the tiering is structured along some measure of resource availability, such as income or the Human Development Index, and for AIDS-related access, sometimes the burden of HIV disease in the country as well. However, the criteria for tiering vary from company to company. Gilead, for example, has established a tiered pricing program for AIDS medicines. For countries with a GNI of less than \$1000 and/or “an extremely high burden of HIV,” the lowest tiered price of Truvada and Viread are available.⁵⁹ The three remaining tiers show discounts below full price in step with lower GNI levels. For ViiV Healthcare (Pfizer and GSK), HIV/AIDS drugs are made available at not-for-profit prices in least developed countries, the World Bank’s low-income countries and all of Sub-Saharan Africa. In middle-income countries, drug prices balance access concerns with commercial objectives.⁶⁰

Depending on where one draws the line, tiering arrangements may offer few price concessions for regions like Latin America. Tiered pricing available for Haiti may not be so for Brazil. Sub-regional negotiations led first the Caribbean, then Central American, and later ten other Latin American countries to strike discounts on AIDS drugs and diagnostic tests.⁶¹ The greatest price reductions occurred using pre-qualified generic sources of ARVs, and importantly, such prices may provide a useful reference benchmark, sometimes well below even the lowest tiered price offered by originator, brand-name firms.

Multinational companies can sometimes be reluctant to offer the lowest tiered price to middle-income countries or emerging economies like China, India or Brazil—markets with significant numbers of potential paying customers. Selecting which countries belong to which tier is a key consideration. The tension over how to treat middle-income countries in tiered pricing schemes has surfaced repeatedly in recent years. PAHO’s efforts to secure discount pricing for

55 US Food and Drug Administration, Implementation of the Biologics Price Competition and Innovation Act of 2009. Available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm>

56 IFPMA, Accelerating Access Initiative, available from: <http://www.ifpma.org/index.php?id=3754>

57 OECD. Pharmaceutical Pricing Policies in a Global Market. Executive Summary, 2008, p. 11.

58 OECD. Pharmaceutical Pricing Policies in a Global Market. Executive Summary, 2008, p. 11.

59 Gilead, “Enabling Access to Treatment,” available from: http://www.gilead.com/enabling_access (Last accessed 28 April 2011).

60 GlaxoSmithKline. HIV/AIDS & ViiV Healthcare: 2010 Corporate Responsibility Report. Available from: <http://www.gsk.com/responsibility/cr-report-2010/access-to-medicines/hiv-aids-and-viiv-healthcare>

61 Fitzgerald, J., and B. Gomez. 2003. An Open Competition Model for Regional Price Negotiations Yields Lowest ARV Prices in the Americas. Presentation to the 8th World STI/AIDS Congress, Punta del Este, Uruguay.

vaccines in Latin America have come into conflict with the Global Alliance for Vaccines and Immunizations' (GAVI) efforts to obtain the lowest possible price for least developed countries.⁶² Since PAHO covers a region with only one LDC – Haiti – their procurement requirement that they must receive the lowest available price on a vaccine has made it difficult for vaccine suppliers to offer GAVI a better price.

However, the growing reality is that most of the global poor—those living under \$1.25 per capita per day – do not reside in countries classified as the least developed.⁶³ While a couple decades ago 93% of the poor lived in low-income countries, today 72% live in middle-income countries. While they are concentrated in populous countries like China, India, Indonesia, Pakistan and Nigeria, the ranks of the poor in other middle-income countries have tripled over this period. This has also given rise to tiering approaches that divide markets within a single country. A preferential price might be offered to the public sector, but not the private sector within a country's healthcare system. Such an approach risks arbitrage between the public and private sector, but also may ignore the reality of how patients in the public sector may be accessing their medicines through out-of-pocket payments in the private sector. The sizeable role of the church-based healthcare system in Africa further blurs the utility of this distinction, separating those who have access from those who have not.

3.2 Alternative approaches to tiering

Tiering does not have to be just over price: it can be applied at different points in the value chain between benchtop and bedside, by granting use of a resource like a compound library for R&D or royalty-free licenses to a product for neglected diseases in developing countries.

Tiered treatment can also apply to regulatory drug approval. Pursuing drug approval through stringent drug regulatory authorities in Western countries has its advantages—clear protocols and regulatory guidance as well as tax breaks, patent term extensions and market or data exclusivity. However, Western regulatory authorities may not require clinical trial data appropriate for scale-up in developing countries, where patients may have very different co-morbid conditions or even different endemic strains. ARVs may be available as generics in developing countries, but not in the markets of Western drug regulatory authorities. Consequently, several regulatory pathways have emerged that allow tiered treatment of drugs for neglected diseases for developing countries: 1) Article 58, a pathway created by the European Commission in collaboration with WHO, allows for a scientific assessment comparable to that done for medicines used in the EU, but for medicines to be used outside of the EU; 2) U.S. FDA's expedited pathway for approving HIV drugs to be purchased for PEPFAR use outside of the United States; and 3) WHO Drug Prequalification, which focuses on the review of products for HIV, TB and malaria (most of which have been for generic drugs for HIV).⁶⁴

3.3 Pooling

Many pharmaceutical products involve multiple components, each of which may be covered under IP protection. Patents, data or market exclusivity placed on these components mean that researchers or manufacturers have to secure licensing of these inventions. Several factors can further increase the complexity of such licensing. Where multiple components are involved, the transaction costs of assembling what might be necessary for commercialization can be substantial.

Consider the patent landscape, commissioned by the Malaria Vaccine Initiative, of the top ten antigens for a malaria vaccine. The landscape uncovered 167 patent families filed by 75 different organizations. Narrowing this down to 39 moderate to high priority patents for developing a vaccine for malaria, most of these priority patents (69%) were found to be held originally by public organizations. By the time the patent landscape was being conducted, nearly half of these priority patents were no longer available for licensing.⁶⁵ These findings suggest that effective pooling require contribution and participation by universities and public research institutions, that pre-existing licensing arrangements with private companies may fail to safeguard potential uses in developing country markets, and that the patent landscape itself may require greater transparency.

Patent obstacles can slow the introduction of technologies, even in industrialized countries. With 2.1 million people tested for HIV in public clinics in the United States, a third were not returning for results. Though rapid tests for HIV were

62 Wilson, Paul. Giving developing countries the best shot: An overview of vaccine access and R&D. Oxfam and MSF, April 2010. Available from: <http://www.doctorswithoutborders.org/publications/reports/2010/MSF-Oxfam-Vaccine-Report.pdf>

63 Sumner, Andy. "The Next Bottom Billion: What If Most of the World's Poor Live in Middle-Income Countries?" CGD Brief. Washington, DC: Center for Global Development, 2011.

64 Moran, Mary, Strub-Wourgaft, Nathalie, Guzman, Javier, Boulet, Pascale, Wu, Lindsey, Pecoul, Bernard. Registering New Drugs for Low-Income Countries: The African Challenge. *PLoS Med* 2011; 8(2): e1000411. doi:10.1371/journal.pmed.1000411

65 Shotwell SL. 2007. Patent Consolidation and Equitable Access: PATH's Malaria Vaccines. In *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (eds. A Krattiger, RT Mahoney, L Nelsen, et al.). MIHR: Oxford, U.K., and PIPRA: Davis, U.S.A. Available online at www.ipHandbook.org.

introduced years earlier in other countries, their use in the United States was significantly delayed because of reported difficulties in licensing the necessary patents, including HIV-2.⁶⁶ Without this, manufacturers were unable to introduce a diagnostic test capable of detecting both HIV-1 and HIV-2 strains.

Pooling can lower the transaction costs of assembling components important to technologies to combat AIDS. Upstream in the R&D pipeline, such components include reagents, research tools, and building blocks for diagnostic tests or for vaccines. Downstream in the R&D pipeline, these components may be drugs used in combination therapies. Collectively, pooling can also help build a research commons.

Overcoming these transaction costs requires some upfront investment. Building institutional repositories of such components can facilitate the development of new technologies. For example, the U.S. National Institutes of Health AIDS Research & Reference Reagent Program has become a source for public distribution of over 8,786 reagents for HIV, many not commercially available.⁶⁷ With over 2500 registered scientists from 80 countries, reagents are sent the world over to academic and industry scientists. Along similar lines, the U.S. National Institute of Allergy and Infectious Diseases created the Reagent Resource Support for AIDS Vaccine Development Program, so that those evaluating vaccinated subjects in clinical testing would have working quantities of common reagents essential for AIDS vaccine development. The standardization of the quality of such reagents supplied under this Program also helps to ensure reproducibility and comparability of findings among research groups working in this area.⁶⁸

Whereas the electronics industry has a track record of patent pooling for standards like MP3 and DVD players, such pooling in biomedicine breaks new ground. Addressing patent holdouts, mitigating anticompetitive concerns, and setting acceptable remuneration levels also must be worked out in constructing a pool. There are financial and non-financial incentives for participating in a pool. Founded in 2002, IAVI's HIV Neutralizing Antibody Consortium sought to tackle a key challenge in AIDS vaccine design—how to trigger antibodies that would neutralize a broad range of HIV strains. The Consortium has institutional members, each entering an agreement to provide the option for IAVI to license any invention from the consortium's research with the purpose of ensuring that resulting vaccines would be accessible and affordable in developing countries.⁶⁹ Such a consortium pools its resources, including intellectual property, towards a common mission.

3.4 Patent pools

Building on a proposal by Médecins sans Frontières and Knowledge Ecology International, UNITAID launched the Medicines Patent Pool (MPP) with a focus on HIV/AIDS medicines. The MPP seeks to negotiate with patent holders to extend voluntary licenses that might help other producers to bring affordable generic medicines for AIDS to market. The MPP hopes that lowering these transaction costs for creating new fixed-dose combinations might allow for more low-cost, quality treatments and pediatric formulations for developing countries. Such fixed-dose combinations might improve adherence and diminish the emergence of drug resistance, while other formulations might yield medicines not requiring a cold chain for storage, suited for developing country needs. With the entry of more generic combinations into the marketplace, the Pool anticipates that competition will result in closer to marginal cost pricing. Still early in its development, the MPP has secured a royalty-free, non-exclusive license to darunavir from the U.S. National Institutes of Health for low- and middle-income countries as defined by the World Bank, but the licensing of additional darunavir patents held by Johnson & Johnson/Tibotec will be required to enable manufacture of the ARV.⁷⁰ ⁷¹ ⁷² Johnson & Johnson/Tibotec has instead opted to conduct direct contracting with generic manufacturers in India and sub-Saharan Africa for supplying darunavir. In so doing, the company maintains that “through these agreements we manage and achieve the multiple components of HIV drug access including timely registration, supply chain development, lower prices, medical education and safety pharmacovigilance.”⁷³ Some companies, however, such as F. Hoffman-LaRoche,

66 Anand, Geeta. Abbott, OraSure Reach Deal on Distribution of AIDS Test. Wall Street Journal, June 17, 2002.

67 “NIH AIDS Research & Reference Reagent Program,” Pathogenesis and Basic Research Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases, available from: https://www.aidsreagent.org/about_program.cfm

68 “HIV/AIDS Vaccine Reagent Resource,” National Institute of Allergy and Infectious Diseases, available from: <http://www.niaid.nih.gov/topics/hivaids/research/vaccines/resources/reagent/Pages/default.aspx>

69 International AIDS Vaccine Initiative, “IAVI launches Neutralizing Antibody Consortium to accelerate search for preventive AIDS vaccine,” News Release, July 9, 2002.

70 Public Health Service, Non-Exclusive Patent License Agreement, available from: <http://keionline.org/sites/default/files/NIH-MPPF-Patent-License-Full-Executed-Sept2010.pdf>

71 Medicines Patent Pool. Questions and Answers: The US National Institutes of Health (NIH) License to the Medicines Patent Pool, September 2010. Available from: http://www.unitaid.eu/images/news/patentpool/20100930_nih_license_q%26a_en.pdf

72 Médecins sans Frontières. NIH Entry Into Medicines Patent Pool is a Welcome First Step, 30 September 2010. Available from: <http://www.doctorswithoutborders.org/press/release.cfm?id=4768&cat=press-release>

73 Letter from Will Stephens, Vice President, Global Access and Partnerships, Johnson & Johnson to Medicines Patent Pool, January 31, 2011. Available from: <http://www.medicinespatentpool.org/content/download/330/2120/version/1/file/J%26J%3ATibotec+Letter+to+Medicines+Patent+Pool.pdf>

Boehringer-Ingelheim, Bristol-Myers Squibb, Sequoia Pharmaceuticals, and ViiV Healthcare (a joint venture between GlaxoSmithKline and Pfizer) have entered negotiations with the MPP, but others such as Merck have announced that they are not prepared to do so.

The potential application of tiering in pooling arrangements has stirred significant debate, including in negotiations over pooling arrangements for AIDS drugs. In discussing the MPP concept, Gilead had maintained that its tiered pricing program, coupled with generic manufacturing partnerships, responds to access concerns. Gilead had a network of partners supporting registration, product distribution and medical education. Having entered directly into licensing agreements with over a dozen Indian companies, Gilead had enabled generic manufacture of active pharmaceutical ingredients and finished tablets of any tenofovir-based fixed-dose combination or pediatric formulation. On a royalty-free basis, the Indian companies were free to sell the API within India, and on the finished product, the companies paid a 5% royalty to Gilead when distributed within India or any of 94 least developed countries.⁷⁴

A direct benefit of the groundwork by the MPP is the enhanced transparency over patent holdings, and in recently releasing an on-line database of the patent status of selected ARVs in low- and middle-income countries, the MPP takes an important step to shedding light on information key to procurement agencies.⁷⁵ First-generation ARVs were patented primarily in high-income countries, but by contrast, newer ARVs are now being patented routinely in countries with domestic pharmaceutical manufacturing capacity, such as China, India, and Brazil.⁷⁶ This has heightened concerns that the MPP ensure that voluntary licenses struck with companies include these middle-income countries, where not only the majority of the poor, but also significant numbers of people living with HIV/AIDS reside. The inclusion of middle-income countries is not only an issue of affordable access, but also one of ensuring a market of sufficient size to scale generic production sustainably.

These concerns resurfaced with the announcement in July 2011 of a breakthrough agreement, the first with a pharmaceutical firm for the MPP.⁷⁷ Under the arrangement, Gilead Sciences committed to licensing tenofovir, emtricitabine, two HIV drugs under development (elvitegravir and cobicistat), and the Quad, a four-drug combination of these drugs. While limiting manufacture to Indian drug firms, the licensing arrangements expanded the geographical scope of where products produced under this license might be distributed. Under this license, tenofovir will be available in more countries than before, but Gilead committed to fewer countries for the new drugs still under development. Notable among the countries excluded from any of the licenses though were several middle-income countries, including Brazil, China, Indonesia and Thailand.

Apart from restrictions on the geographic scope of the licenses, another point of contention is the payment of royalties. The MPP negotiated a royalty rate of 3-5% for Gilead, from which it would receive 5%. While only a token amount (0.15-0.25% of the generic price), it might not go a long way to ensuring financial sustainability of the MPP, but will make it accountable for justifying that the value-added benefit from lowering transaction costs outweigh the costs of administering the MPP. The MPP importantly has made the licensing arrangements with Gilead transparent. This sets a useful precedent, but may also anchor future negotiations. The licenses reveal the complexity of these arrangements. Significantly, the MPP-Gilead agreement calls for a waiver of royalties for pediatric formulations, provisions enabling licensees to supply countries availing themselves of TRIPS flexibilities such as compulsory licenses, and a waiver of data exclusivity rights. The companies, in turn, receive a royalty-free grant back on improvements.

Transfer of know-how may be without strings attached, but in fact, termination of a license includes all combination products containing that drug. The licenses for each of these drugs, it is argued, are severable, but will Gilead's willingness to share tacit knowledge in producing these follow-on products be equally generous with those who choose to honor some patents, but dispute others?

While the focus of the MPP is on combination AIDS treatments, the Gilead licenses open the door to related indications of these products, such as hepatitis B for tenofovir and any future, approved indication for elvitegravir and cobicistat. But there are concerns of this being a double-edged sword – it has been argued that this would be equivalent to extending patent recognition to secondary indications that would otherwise not be accepted in India.⁷⁸ The response from the

74 Alton, Gregg. "Gilead's Access Program and the UNITAID Patent Pool", Presentation at University of California, Berkeley School of Law conference on Patent Pools, 6 November 2009. Available from: http://www.law.berkeley.edu/files/12_alton.pdf

75 "The Patent Status Database for Selected HIV Medicines," Medicines Patent Pool, available from: <http://www.medicinespatentpool.org/LICENSING/Patent-Status-of-ARVs>

76 UNITAID Patent Pool Initiative: Implementation Plan (Executive Summary). November 2009. Available from: http://www.medicinespatentpool.org/content/download/215/1231/version/1/file/ForWebsite_UNITAID_Patent_Pool_Implementation_Plan_-_Executive_Summary.pdf

77 Licenses with Gilead Sciences for tenofovir, emtricitabine, cobicistat, and elvitegravir and the "Quad," Medicines Patent Pool, July 2011. Available from: <http://www.medicinespatentpool.org/LICENSING>

78 ITPC & I-MAK. "The Implications of the Medicines Patent Pool and Gilead Licenses on Access to Treatment", Briefing Paper, 2011. Available from: http://www.itpcglobal.org/images/itpc_i-mak_the_broader_implications_of_the_mpp_and_gilead_licenses_on_access_final_25-7-2011.pdf

MPP however is that: "(I)f a patent licence for a compound that has known therapeutic benefit for both HIV and HBV limited the field of use only to HIV, that would mean that it would be a contractual violation for a generic company to market that medicine for the treatment for HBV. This would mean that generic companies would be prohibited from supplying the same drug to the millions of people who are living with HBV, and also reduce the scope for greater economies of scale that is created by a larger potential market for that drug."⁷⁹ It is also likely that future challenges might surface over new use patents for elvitegravir and cobicistat.

Beyond the issues of patents and prices, licensing agreements struck by the MPP can have real potential to influence control over the supply chain. From the sourcing of the API to where generic manufacture may occur or not for these licensed drugs, the implications extend to the combination products of which these licensed drugs are part. So how parallel importation or restrictions on third party resellers is handled under this agreement will shape its impact on the global AIDS drug supply. The complexity of the Gilead agreement reveals both the strengths and shortcomings of voluntary measures. As civil society debates the precedent set by its first license with a pharmaceutical company, the MPP's organizers caution that pooling of IP should be seen as only one strategy to be used in tandem with others, not a panacea for innovation and access.

Part IV. Financing innovation for access

Global funding for AIDS has risen six-fold from 2002 through 2008, reaching US\$15.6 billion in 2008. But with the flatlining of funding since 2009, the resource gap for AIDS continues to mount, up to US\$7.7 billion in 2009.⁸⁰ Public funding rose as generic competition over AIDS medicines lowered treatment costs and thereby enabled scale-up of treatment. Over time, companies developing new AIDS medicines have patented more broadly, particularly in developing countries with manufacturing capacity. Absent significant price breaks for these settings, medicine prices will again stand in the way of access.

It is beyond the scope of this paper to examine systematically the full range of financing mechanisms for innovation. However, the influence of these approaches on the sharing of knowledge for continued innovation and greater access to health technologies for HIV/AIDS might be described here. The public's stewardship over intellectual property rights must ensure fair returns from the public's investment in R&D. Failing to address these issues today risks repeating yesterday's lessons tomorrow. The details of how these financing mechanisms are structured can make a pivotal difference.

4.1 Push mechanisms: Financing R&D

Push mechanisms, such as research grants and R&D tax credits, diminish the risk of R&D. By paying for inputs, push mechanisms provide an opportunity to de-risk the R&D pipeline for innovation of next generation drugs, diagnostics and vaccines for AIDS.

By lowering barriers to entry—or de-risking the pipeline—public funding may obviate the need for exclusive licensing. At its limit, public funding can lessen the need for private sector capital, particularly when there are no paying markets. The Drugs for Neglected Diseases Initiative has brought six new treatments for neglected diseases to market. For example, in developing the antimalarial combination of artemisinin and mefloquine, DNDi bypassed the customary value chain of pharmaceutical production and partnered with the Brazilian public pharmaceutical company, Farmanguinhos/Fiocruz, and arranged the South-South transfer of this technology to Cipla, an Indian generic firm. In collaboration with Anacor Pharmaceuticals and SCYNEXIS, DNDi also announced the successful completion of pre-clinical studies of a potential breakthrough therapy for human African trypanosomiasis, or sleeping sickness. SCYX-7158 represents a novel class of boron-containing compounds.⁸¹ With financial support from the Gates Foundation, *Médecins sans Frontières* and government funders, DNDi and its private sector partners completed the lead optimization and preclinical studies for US\$14.8 million.⁸²

Particularly for drugs and vaccines, clinical trials represent the largest component of R&D costs. Though it may be a public good to test new combinations of ARVs or pediatric formulations, the promise of markets where the products would

79 The Medicines Patent Pool/Gilead Licenses: Questions and Answers. Medicines Patent Pool, Updated August 2011. Available from: <http://www.medicinespatentpool.org/LICENSING/Current-Licences/Medicines-Patent-Pool-and-Gilead-Licence-Agreement/Q-and-A-Gilead-Licences>

80 Kates, Jennifer, Boertz, Kim, Lief, Eric, Avila, Carlos and Gobet, Benjamin. "Financing the Response to AIDS in Low- and Middle-Income Countries: International Assistance from the G8, European Commission and Other Donor Governments in 2009." Kaiser Family Foundation, July 2010. Available from: <http://www.kff.org/hiv/aids/upload/7347-06.pdf>

81 Jacobs RT, Nare B, Wring SA, Orr MD, Chen D, et al. (2011) SCYX-7158, an Orally-Active Benzoxaborole for the Treatment of Stage 2 Human African Trypanosomiasis. *PLoS Negl Trop Dis* 5(6): e1151. doi:10.1371/journal.pntd.0001151

82 Drugs for Neglected Tropical Diseases Initiative. "Innovative Partnership Advances Novel Drug Candidate to Combat Sleeping Sickness," Press Release, June 28, 2011. Available from: <http://www.dndi.org/press-releases/892-oxaborolesbio.html>

need to be priced close to marginal cost may not be sufficiently attractive to draw substantial private sector investment. Clinical trials as a public good, but funded as a private good, risk being undersupplied. The public funding of clinical trials may lower the barrier for firms to bring such products to market. Other reasons also compellingly justify the need for greater public funding of clinical trials. A system for independent funding of such trials may reduce potential bias in study design, ensure greater transparency of test data and R&D costs, and encourage both R&D for diseases of public health priority and for treatments that might induce therapeutic competition.⁸³ Innovative financing mechanisms, such as UNITAID's solidarity tax on airline tickets, could support a cross-national source for supporting such a strategic push mechanism. The WHO Consultative Expert Working Group on Research and Development's call for a binding global commitment on all countries to commit at least 0.01% of GDP to government-funded R&D—thereby doubling current investments—could similarly finance such a mechanism.⁸⁴

4.2 Push mechanisms: Licensing for Innovation and Access

Apart from paying for inputs of R&D, however, the licensing of key patent protected building blocks for R&D plays an equally important role. While the overall contribution of academic patents to new drug applications is not preponderant, AIDS drugs that were new molecular entities were far more likely to have academic patents (one out of four) compared to non-AIDS drugs (6.7%).⁸⁵ Translating such innovation into practice will benefit from the public sector's strategic use of IP.

Reflecting back on this experience, the NIH Office of Technology Transfer observed that: "On one hand, it can be quick and expedient to grant a single exclusive license for all fields of use; on the other hand it is important (especially for publicly funded research) to have the technology made available to as many possible users for as many possible applications."⁸⁶ For research reagents or diagnostics, the patented technology is typically part of any resulting product or service. For drug development, the patented technology might be either tool or component of the resulting product. According to the specific case, NIH has tailored the license to be non-exclusive or, if need be, exclusive; and the royalty, perhaps an upfront, single payment to avoid stacking where multiple components are involved. Growing out of these practices has come normative guidance, such as the NIH Research Tools Policy and Best Practices for Licensing Genomic Inventions.⁸⁷

In 2001, at the urging of students, faculty and its inventors, Yale University urged Bristol-Myers Squibb to reduce the price of stavudine (d4T), and the company relented by agreeing not to enforce the patent in sub-Saharan Africa.⁸⁸ The same company licensed two patents on ddl, an ARV originally patented by the U.S. National Institutes of Health in 1988, and then sought a patent, at first unsuccessfully, for an improved oral dosing formulation of ddl, based on adding a buffer (antacid) in Thailand.⁸⁹ Ten years later, Bristol-Myers Squibb was granted a patent that had been irregularly amended to cover all dosage forms of ddl (instead of just one dosage form), effectively blocking Thailand's Government Pharmaceutical Organization from manufacturing or procuring generic ddl, except in a powder formulation that was both difficult to administer and caused more gastrointestinal side effects. This prompted a protracted legal challenge that resulted in the amendment of the patent being declared invalid.⁹⁰ Had public licensing set reach-through conditions on this drug for those in developing countries, perhaps this situation might have been averted.

Between the NIH's licensing of ddl and darunavir, the opportunity for the public sector's strategic use of intellectual property has grown considerably. In the mid-1990s, the NIH Office of Technology Transfer encouraged its industry partners to commit to the White Knight clause—a voluntary, unwritten but oral agreement to "do good" for the community, recognizing the taxpayer's contribution, on an exclusive license anticipated to be profit-making. The clause, so named after the first company that discussed the possibility, has resulted in various forms of paybacks, from supplying drugs for clinical trials and vaccines for schools to ensuring indigent access to health facilities.⁹¹ Such exhortations have

83 Lewis, Tracy R, Reichman, Jerome H, So, Anthony D. The Case for Public Funding and Public Oversight of Clinical Trials. *Economists'Voice*, January 2007.

84 Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination. *Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination*. Geneva, Switzerland: World Health Organization, April 2012. Available from: http://www.who.int/phi/CEWG_Report_5_April_2012.pdf

85 Sampat, Bhaven. Academic Patents and Access to Medicines in Developing Countries. *Am J Public Health* January 2009; 99(1): 9-17

86 Keller, George H. and Ferguson, Steven M. Commercial Licensing of HIV-1 Protease: Applications of the NIH Research Tools Policy. *J Biolaw & Business* 2009; 12(4): 1-5.

87 National Institutes of Health (NIH), Public Health Service, U.S. Department of Health and Human Services. Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice. Federal Register Notice, December 23, 1999. Available from: http://www.ott.nih.gov/policy/rt_guide_final.html

88 DeYoung, Karen and Brubaker, Bill. "HIV Drug Price Cut for Some in Africa," *Washington Post*, March 15, 2001, p. A01.

89 Kuanpoth, Jakkrit. Patents and Access to Medicines in Thailand: The ddl case and beyond. *Intellectual Property Quarterly* 2006; 2: 149-159.

90 Ford, Nathan, Wilson, David; Bunjumngong, Onanong & von Schoen Angerer, Tido. The role of civil society in protecting public health over commercial interests: lessons from Thailand. *The Lancet*, Vol 363, February 14, 2004

91 Coulombe, Margaret. "Who Was that White Knight?" *The NIH Catalyst*, November-December 2000. Available from: <http://www.nih.gov/catalyst/2000/00.11.01/page5.html>

since taken clearer shape in the written terms of licenses and in normative guidance for technology transfer.

The American Association for the Advancement of Science's Project on Science and Intellectual Property in the Public Interest, with Rockefeller and MacArthur Foundation support, put together a starting inventory of humanitarian access licensing provisions.⁹² These provisions span from patent donation to conditions of licensing that touch on non-exclusivity, royalties and remuneration, field limitations, reservation of rights for research or reach-through, and affordable pricing.

In releasing a call for proposals to develop point-of-care diagnostics for monitoring AIDS, the Doris Duke Charitable Foundation considered carefully how its grant agreements might help ensure downstream licensing and affordable access to the fruits of its funded research. Building in such conditions into its grant agreements, the Foundation retained a royalty-free, non-exclusive license to patents filed in developing countries on inventions emerging from its funded research. By keeping the option of sub-licensing to make and distribute the product if the grantee failed to deliver, the Foundation sought to ensure its charitable objective of delivering the technology at an affordable cost in these resource-limited settings.⁹³

Universities as publicly funded institutions can also play a significant role in humanitarian access licensing. Under its Socially Responsible Licensing Program, the University of California, Berkeley has negotiated contracts enabling royalty-free distribution of a handheld MEMS immunodiagnostic assay in various developing countries by the Sustainable Sciences Institute and of a TB vaccine outside certain industrialized countries as well as a revenue-sharing arrangement with the Commonwealth of Samoa in return for access to an indigenous natural product that may have antiviral properties.⁹⁴ Even under exclusive licenses, Berkeley has pursued mandatory sub-licensing clauses, whereby if unanticipated uses of IP arise, the licensee is bound either to pursue the indication or to allow others to do so under sublicense.⁹⁵

Making social returns on humanitarian access licensing tangible is key. At the University of California, Berkeley, these returns are both financial and reputational. To capture double bottom-line gains, new metrics—of which licensing revenue is only one measure—may be needed. By placing the technology transfer office under a broader umbrella—Intellectual Property and Research Alliances—the University can more effectively weigh what might be a revenue loss in the eyes of the technology transfer office against a offset gain in reputation or in grant funding for the University's research.

Domestic laws also shape such institutional norms. Laws like the U.S. Bayh-Dole Act have encouraged the patenting of publicly funded research in hopes of enhancing its commercialization, but perhaps with some unintended consequences on the role of universities in generating and sharing knowledge. The search for the blockbuster success has created a "lottery ticket" mentality, where licensing revenues have not kept pace with the costs of pursuing university patents and where social returns from publicly funded research may not receive their due. Thirty years after the U.S. Bayh-Dole Act's enactment, revenues from technology licensing account for less than 5% of academic research dollars at U.S. universities and research institutions, and most of these revenues are in the hands of a few universities with patents on "blockbuster" inventions. Yet this has not arrested interest in some developing countries to emulate blindly the adoption of Bayh-Dole legislation, too often without sufficient safeguards for the public's interest in securing fair returns from such government investment.⁹⁶

In recent years though, the call for greater attention to these concerns in university-industry licenses has been repeatedly made, initially through the student-organized Philadelphia Consensus Statement on University Policies for Health-Related Innovations in 2006 and later addressed, in part, by technology transfer offices.^{97, 98, 99} The 2007 statement

92 Brewster, Amanda L, Chapman, Audrey R., and Hansen, Stephen A. Facilitating Humanitarian Access to Pharmaceutical and Agricultural Innovation. *Innovation Strategy Today* 2005. 1(3): 203-216. Available from: <http://www.biodevelopments.org/innovation/ist3.pdf>

93 Doris Duke Charitable Foundation. 2004. Medical Research Program Bulletin. Available from: http://www.ddcf.org/doris_duke_files/download_files/MRPBulletinOct04.pdf

94 Mimura, Carol. Technology Licensing for the Benefit of the Developing World: UC Berkeley's Socially Responsible Licensing Program. *Journal of the Association of University Technology Managers*. YEAR : 15-28.

95 Institute of Medicine. *Venture philanthropy strategies to support translational research: Workshop summary*. Washington, DC: The National Academies Press, 2009.

96 So, Anthony D, Sampat, Bhaven N, Rai, Arti K, Cook-Deegan, Robert, Reichman, Jerome H, Weissman, Robert, and Kapczynski, Amy. Is Bayh-Dole Good for Developing Countries? Lessons from the US Experience. *PLoS Biology* 2008; 6(10): e262. doi:10.1371/journal.pbio.0060262

97 Universities Allied for Essential Medicines. *Philadelphia Consensus Statement on University Policies for Health-Related Innovations, 2006*. Available from: <http://essentialmedicine.org/cs/>

98 In the Public Interest: Nine Points to consider in Licensing University Technology, 2007. Available from: <http://otl.stanford.edu/documents/whitepaper-10.pdf>

99 Statement of Principles and Strategies for the Equitable Dissemination of Medical Technologies. Available from: <http://www.autm.net/Content/NavigationMenu/TechTransfer/GlobalHealth/statementofprinciples.pdf>

from a group of university technology transfer offices, “In the Public Interest: Nine Points to consider in Licensing University Technology,” highlights several important principles, from reserving the right to practice licensed inventions for universities and other non-profit and governmental organizations to ensuring broad access for research tools. The ninth and final point calls upon its signatories to “consider including provisions that address unmet needs, such as those of neglected patient populations or geographic areas, giving particular attention to improved therapeutics, diagnostics and agricultural technologies for the developing world.” Perhaps a useful tenth point might have been on enforcement and monitoring, but that was not to be. Building on this, the Harvard-led Statement of Principles and Strategies for the Equitable Dissemination of Medical Technologies goes somewhat further.

This succession of statements from the U.S. university community suggests norms are shifting to recognize humanitarian access concerns. Such university licenses can help shape norms for sharing inventions from publicly funded research and set useful precedents. But how can accreting access gains for developing countries, university license by license, add up to greater institutional and system-wide, sustainable changes?

Some of these licensing arrangements are easy to strike, and others less so. Where the licensee anticipates little revenue impact, negotiating such arrangements may be pro forma. Accepting a license limited by geography, indication or both, a small firm might have no aspiration of applying the patent for a neglected disease indication in a developing country. Such tiered arrangements create a dual market, and the willingness of a firm to forsake significant profit-taking from one market segment is inversely proportional to the ability of that market to pay. Going further, the dual market also provides an opportunity to cover the research premium in the more lucrative market segment and to allow the market segment receiving preferential treatment to free ride on this investment. For AIDS though, is the gradient between the segments of this dual market eroding away, with a market that is increasingly public sector funded and a burden of disease that continues to shift to developing countries?

4.3 “Push and pool”

Public sector and philanthropic funding can strategically leverage such opportunities to bring technologies to market for those in developing countries. An instructive example comes from the work of the University of California, Berkeley. With NIH grant support, Professor Jay Keasling developed a microbial synthesis process with the potential of providing a non-seasonal supply of artemisinin to treat malaria. The University struck an innovative license with Amyris Biotechnologies, where Dr. Keasling also served as Chief Scientist, and the Institute for OneWorld Health (IoWH). The University extended a royalty-free license to both Amyris and IoWH for applying this technology towards the production of artemisinin for the treatment of malaria in developing countries.¹⁰⁰ In return, Amyris would produce artemisinin at no profit for this indication. The Gates Foundation supported this arrangement with an initial \$42.6 million grant, of which \$8 million went to UC Berkeley and \$10 million went to Amyris Biotechnologies. For the company, this was non-diluting cash, that is, the company did not have to sell any equity shares to raise this capital. By using philanthropic capital, it could bootstrap its proof of concept of this early stage technology to this project. Later the same technology might have dual use for biofuels, fragrances and perfumes, all of which are potentially lucrative applications, and equity shares in the company would have greater value in later rounds of venture capital fundraising.

With another \$10 million Gates Foundation grant and assistance from Sanofi-Aventis, IoWH is now entering the production and distribution phase of this semisynthetic product. For Sanofi-Aventis, several potential benefits accrue: 1) the opportunity of winning an FDA priority review voucher for bringing a neglected disease product to market (AIDS is not one of the 16 diseases covered under this program, but malaria is); 2) experience in navigating the drug regulatory systems in disease-endemic countries, building goodwill with the first step being a humanitarian access initiative; 3) market presence and entry in these countries; and 4) the double-bottom line social return of reputational gain.¹⁰¹ This example serves to illustrate how public sector or philanthropic funding, coupled with strategic licensing arrangements, could seed new breakthrough business models for bringing needed treatments to the developing world.

Moving beyond the case-by-case application of humanitarian access licensing, pooling arrangements offer an institutional vehicle by which these measures become the norm. Collectively, pooling can support the creation of a research commons. A research commons would ensure greater access to the building blocks of knowledge and innovation. Building on what is already in the public domain, funders, research institutions, scientists and others could work to ensure that data, journal publications, material reagents, and inventions were made more freely available for scientific exchange and development. Contributing to the research commons, some inputs might become available

100 \$42.6 Million, Five-Year Grant from Gates Foundation for Antimalarial Drugs Brings Together Unique Collaboration of Biotech, Academia, and Nonprofit Pharma. 2004. Institute for OneWorld Health Press Release. Available from: http://www.oneworldhealth.org/documents/DP_%20Malaria%20Release%20121304.pdf

101 Mimura, Carol. “Nuanced Management of IP Rights: Shaping Industry-University Relationships to Promote Social Impact,” in *Working Within the Boundaries of Intellectual Property*, edited by Rochelle Dreyfuss, Harry First, Diane Zimmerman. Oxford University Press, 2010. Available from: <http://innovate.ucsb.edu/wp-content/uploads/2010/04/Mimura-SSRN-id1434545.pdf>

through the strategic use of IPRs. In the Human Genome Project, the Bermuda Rules required leading genome sequence centers, funded by the U.S. National Institutes of Health and the Wellcome Trust, to deposit every 1000 base pairs on-line into the GenBank, thereby creating a record of prior art deterring patenting of the human genetic endowment. Some part of a research commons inevitably would require arrangements under license—a contractually reconstructed commons¹⁰² - but such licensing can support greater openness and sharing. Other parts of the research commons might come from the decentralized and nonmarket-based production of knowledge, made increasingly possible in a networked information economy.¹⁰³ The FightingAIDS@Home distributed computing project engaged a network of on-line contributors who donated their desktop computing power to conduct a virtual screening of potential compounds that might inhibit HIV protease mutant structures, thereby assisting in the design of new inhibitors that address rising drug resistance.¹⁰⁴ A hybrid of financial and non-financial incentives can be found in the Indian Council of Scientific and Industrial Research's Open Source Drug Discovery (OSDD) Initiative, initially focused on developing drugs for tuberculosis. Using a click-wrap license, contributors grant back rights to their additions and modifications to the OSDD community. They receive credit under a microattribution system—points awarded by peer review for their efforts on work packages on this open source, collaborative platform. These accumulated points can result in non-financial rewards like professional recognition and financial rewards such as milestone prizes. Mobilizing hundreds of volunteers, the OSDD project has already worked on reannotating the TB genome, identified a potential drug target for treating TB, and created an open access repository of 20,000 small molecules being screened for *M. tuberculosis*.¹⁰⁵ Still a young project, the OSDD initiative is a promising alternative pathway to how the scientific community can build a research commons.

4.4 Pull mechanisms

By contrast, pull mechanisms pay for outputs of R&D, thereby ensuring returns on investment. Over the past decade, reimbursement for AIDS treatment has scaled up, and public procurement of AIDS drugs and diagnostic tests has enticed firms to enter the marketplace. Higher volumes, but close-to-marginal cost pricing in developing countries has proven more attractive for generic manufacturers than research-intensive firms. Still the broader registration of patents taken out on newer AIDS medicines suggests that there is interest, on the part of research-based companies, to hold onto the potential of these markets. Accepting dual or differential pricing arrangements, such firms balance concerns over revenues and access. The flatlining of global AIDS funding has also resulted in a much higher percentage of countries reporting ARV treatment programs being adversely affected by the current funding situation, an increase from 11% to 21% in the period between 2008 to mid-2009, and underscored the importance of ensuring affordable access under these tiered pricing arrangements.¹⁰⁶

Pull mechanisms for pharmaceutical R&D have traditionally included various forms of intellectual property protection, from patents to data exclusivity. In recent years, TRIPS has extended the floor of IP protection to emerging economies and middle-income countries. In industrialized countries, data exclusivity for biologics—medicines derived from living cells and now comprising one out of four FDA approvals—tops a decade in Europe and 12 years in the United States. However, the rising tide of intellectual property protections has not been matched by commensurate gains in R&D productivity. In fact, from 1993 to 2004, the industry reported after adjusting for inflation that R&D expenses climbed 147 percent. By contrast, the number of new drug approval applications for truly novel medicines increased only 7 percent, and despite approving three-quarters of new drug applications, FDA approvals for new medical entities have actually declined since 1996.¹⁰⁷ Interviews conducted by the U.S. Government Accountability Office also suggested that IP protections rewarding companies to pursue minor changes to existing medicines may actually divert efforts to pursue and reduce incentives to develop innovative products.

Much of the global funding for procurement of AIDS medicines in developing countries comes from the public sector, either government or philanthropic sources.¹⁰⁸ It is beyond the paper's scope to explore potential new sources of funding. Instead the discussion here will focus on how pull mechanisms might be used in tandem with intellectual property rights to ensure optimal innovation and access for AIDS prevention and treatment efforts.

102 Reichman JH, Uhler PF. A Contractually Reconstructed Research Commons for Scientific Data in a Highly Protectionist Intellectual Property Environment. *Law and Contemporary Problems* Winter/Spring 2003; 66: 315-461.

103 Benkler, Yochai. *The Wealth of Networks: How Social Production Transforms Markets and Freedom*. New Haven, Connecticut: Yale University Press, 2007.

104 Chang M, Lindstrom W, Olson AJ, Belew RK. Analysis of HIV Wild-Type and Mutant Structures via in Silico Docking against Diverse Ligand Libraries. *J Chem Inf. Model* 2007; 47: 1258-1262.

105 Council of Scientific and Industrial Research. The Open Source Drug Discovery Update 2010; 1(1): 4-11.

106 UNAIDS, Impact of the global financial and economic crisis on the AIDS response. UNAIDS/PCB(25)/09.26, 28 October 2009.

107 United States Government Accountability Office. New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts, GAO-07-49, November 2006.

108 "Funding for The HIV and AIDS Epidemic," AVERT (AVERTing HIV and AIDS), 2009. Available from: <http://www.avert.org/aids-funding.htm>

The development of AIDS medicines has also received substantial protection under the U.S. Orphan Drug Act, both from push and pull mechanisms, from R&D tax credits and from the seven-year market exclusivity incentive. Over the first decade after the Act's enactment in 1983, of the 19 drugs licensed to treat AIDS and HIV-related diseases, 13 had received orphan drug designation, and 10 benefited from the exclusive marketing rights. Of drugs designated as orphans, nearly 70 targeted HIV-related diseases.¹⁰⁹ Even when targeted to specific neglected disease areas, the challenge with pull mechanisms reliant on market exclusivity is, of course, price. Recently the pricing of two drugs coming under U.S. Orphan Drug Act market exclusivity have stirred concerns of abusive profit-taking. The firm URL Pharma had discovered a new dosing form of colchicine—a drug long known to clinicians as a therapy for gout—for treating familial Mediterranean fever. Upon receiving seven years of market exclusivity for Colcrys, the manufacturer took steps to remove all other versions of colchicine from the market and hiked the price fifty-fold, from US\$0.09 to US\$4.85 per pill.¹¹⁰ Another company, K-V Pharmaceutical Company, also took advantage of Orphan Drug Act market exclusivity for 17-hydroxyprogesterone (Makena). Available since the 1950s, the drug was compounded by pharmacists for the prevention of preterm labor.¹¹¹ It was sold for \$10-15 per shot until K-V received market exclusivity for the drug and began charging \$1,500 per shot. The public outcry prompted the U.S. FDA to announce that it would not enforce the exclusivity against compounding pharmacists supplying the drug, and the company has since dropped its price 55% to \$690 per dose.

4.5 Prizes

Several alternative approaches to structure pull mechanisms have emerged in recent years. Each is a form of prize that pays for outcomes, defined as a prespecified product or as the delivery of health outcomes. In the context of this discussion, the prize approach may also delink R&D investment from return on that investment, for example, by buying out the patent with a lump sum payment and licensing the product for generic production. This approach is particularly attractive when research-intensive companies are not drawn by the high-volume, close-to-marginal cost business proposition that diseases of high prevalence and burden in developing countries present.

Several prize proposals have received significant attention, and their applicability to supporting innovation of technologies to combat AIDS, as a result, raised. They range from an Advance Market Commitment that – at least in its first use – has not conditioned IP in its prize design to the Health Impact Fund that places IP under a license for generic production after a ten-year run-in period. This paper examines further Advance Market Commitments and the Health Impact Fund, with a view to highlighting a number of considerations that should inform the structuring of prizes.

Advance Market Commitments. Advance market commitments (AMCs) provide pharmaceutical firms with a guaranteed, initial purchase price in order to create a potential, viable future market for a product. Supported by a \$1.5 billion commitment, the Gates Foundation along with Canada, Italy, Norway, Russia and the United Kingdom have created an AMC to bring a late-stage pneumococcal vaccine adapted for strains found in developing countries.¹¹² Donors establish a clear target product profile that specifies what vaccine would be clinically effective, set a guaranteed price and provide an AMC subsidy, and define the criteria for participation (the product must be pre-qualified by WHO and deemed eligible by an Independent Assessment Committee for AMC funding). Under this arrangement, a manufacturer agrees to sell at least 10 million doses per year for 10 years with a price up to \$3.50. The Global Alliance for Vaccines and Immunizations supplements this price up to \$3.50, but after the period of AMC subsidy, the price remains at \$3.50. The pneumococcal vaccine AMC encourages first generation suppliers to ramp up manufacturing capacity to meet potential demand and hopes to draw in second generation suppliers that might spur innovation and competition in the marketplace. Under the pneumococcal vaccine AMC, there is no transfer of IP, nor assurances of sharing of IP among contenders for the prize.

The pneumococcal vaccine AMC has come under critical scrutiny.^{113,114} Questions have been raised about the level of the AMC subsidy, plus tail price, of US\$7.00 per initial dose; how best an AMC can successfully recruit follow-on firms, beyond the multinational pharmaceutical firms already well positioned to deliver, to create the hoped-for future marketplace of innovation and competition among suppliers; and how to add future AMCs without locking up public sector funding and thereby limiting the flexibility to scale up other childhood vaccines as the need arises.

109 Arno, Peter S, Bonuck, Karen, Davis, Michael. Rare diseases, drug development, and AIDS: the impact of the Orphan Drug Act. *The Milbank Quarterly* 1995; 73(2).

110 Kesselheim, Aaron S., Solomon, Daniel H. Incentives for Drug Development—The Curious Case of Colchicine. *New England Journal of Medicine* 2010; 362(22): 2045-2047.

111 Loftus, Peter. "K-V slashes Price of Drug Amid Outcry." *Wall Street Journal*, April 1, 2011.

112 GAVI Alliance and World Bank. Advance Market Commitments for Vaccines: Creating Markets to Save Lives, 2010. Available from: http://www.vaccineamc.org/files/AMC_FactSheet2010.pdf

113 von Schoen-Angerer, Tido. Questioning the 1.5 billion dollar vaccine deal. *Development Today*, April 25, 2008. Available from: <http://www.msaccess.org/resources/press-clips/development-today-editorial-on-advance-market-commitment>

114 Light, Donald. Saving the pneumococcal AMC and GAVI. *Human Vaccines* February 2011; 7(2): 138-141.

Also contrasting this pilot AMC with the conjugate meningitis A vaccine, the relative strengths and shortcomings of push and pull approaches must also be considered. Launched with a US\$70 million Gates Foundation grant, the MenAfriVac vaccine will be priced at less than US\$0.50 per dose. While perhaps of different technical complexity than the multivalent pneumococcal conjugate vaccine, the Meningitis Vaccine Project, a partnership between PATH and the World Health Organization, had arranged for the transfer of conjugate vaccine technology from the US FDA to the Serum Institute of India, building capacity in a developing country and ensuring its low-cost production. While reliant and limited to a single manufacturer, one can easily envision how such an approach might be applied to creating a technology hub, like the one for influenza viruses created by the Netherlands Vaccine Institute in collaboration with WHO.¹¹⁵ This technology platform provides technology transfer, training and expertise for multiple manufacturers in low- and middle-income countries. For AIDS technologies, the question will be whether an AMC can provide incentives for R&D, create an enabling environment for that innovation, and ensure affordable pricing more effectively than other push or pull mechanisms.

Prize Fund. Under the proposal for a Prize Fund, four options—each building on the last—are laid out as alternatives to the current pull incentives that rely on IP-based monopolies: 1) mega cash prizes awarded based on the health impact resulting from delivery of the product; 2) a prize system that also offers open source dividends to those who freely share their research data or materials, know how or inventions and contribute to the final products rewarded; 3) building on 1) and 2), a prize system with funding set aside and managed by competitive intermediaries focused on translating scientific discoveries into useful products and resourced based on their success in accomplishing these ends; and 4) a system that effectively swaps exclusive rights for the freedom to use inventions as long as patent holders receive remuneration.¹¹⁶ None of these options are intended to supplant the role of government in offering push incentives. To allocate prizes in proportion to the benefits of usage and efficacy, the valuation of prizes will require much better measures of health outcomes than currently available. The Prizes Fund emphasizes an open licensing approach and importantly seeks to de-link R&D costs from drug prices. Modeled on these principles, U.S. Senator Bernie Sanders has introduced both the Medical Innovation Prize Fund Act (S. 1137) and the Prize Fund for HIV/AIDS Act (S. 1138).

Health Impact Fund. Still a proposal, the Health Impact Fund seeks to incentivize innovation by paying for performance. A participating pharmaceutical firm would commit to providing its drug at the cost of manufacturing. In return, the firm would receive direct payment from the Health Impact Fund annually for ten years. Its share of the pool would be proportional to its share of health impact among the registered products. The Health Impact Fund calls for an initial budget of US\$6 billion, enough to reward 20 drugs with US\$300 million per drug per year.¹¹⁷ Firms would retain their patent rights, but extend zero-priced licenses for the technology needed to manufacture and sell the product following the ten-year period. During the ten-year period, participation in the pool is voluntary, so a firm could elect to exercise its monopoly pricing when that might return greater profits than the Fund might disburse.

A key point of contention between proponents of the Prize Fund and the Health Impact Fund relates to how the Health Impact Fund relies on market monopolies during the first ten years and obliges those voluntarily taking part in the Health Impact Fund to sell their product at close to the average cost of production rather than rely on generic competition. Proponents of the Health Impact Fund point to circumstances when generic competition may not take hold—when the market is not sufficiently attractive to draw in multiple manufacturers, when the barriers to entry are considerable as for complex biologics, and where trade secrecy and proprietary know how also limit follow-on competition. Still a ten-year monopoly period leaves much room for a sole source supplier to charge a high price and collect rewards commensurate to health impact. Since it is voluntary, participating firms would expect to reap greater rewards from the Health Impact Fund arrangement than not and have little incentive to encourage generic competition.

The proposal has also been criticized on the grounds that the financial incentives advantage those products that have a greater impact on reducing the global burden of disease thus biasing R&D towards “low-tech essential drugs,” a proposition not likely to be embraced by industrialized countries critical to footing the bill for this approach.¹¹⁸ Apart from the challenges of counting DALYs and deaths, the availability of the best data, justifying the level of reward received, may be inversely proportional to the health status of the countries most in need. Moreover, would it be fair to fault the innovator for non-market, political factors beyond the firm’s control that limit a drug’s distribution? There also may be significant challenge in finding a consistently reliable and fair approach to apportion rewards among contributors to a combination drug.

115 International Technology Platform for Influenza Vaccines (ITPIV). 2011. Available from <http://flusecure.eu/>

116 Love, James, Hubbard, Tim. Prizes for Innovation of New Medicines and Vaccines. *Ann Health Law* 2009; 18(2): 155-186.

117 Hollis A, Pogge T. *The Health Impact Fund: Making New Medicines Accessible for All*. Incentives for Global Health, 2008.

118 Sonderholm, Jorn. A Reform Proposal in Need of Reform: A Critique of Thomas Pogge’s Proposal for How to Incentivize Research and Development of Essential Drugs. *Public Health Ethics* 2010; 3(2): 167-177.

4.6 A hybrid approach

Not all prizes are created equal. The details of prize competitions matter. How long is the distance between start and finish? How is remuneration handled under the prize? Who gets to run the race for the prize?

This distance from bench to bedside is typically shorter for a diagnostic, but longer for a drug or vaccine. If the distance between start and finish is great, those competing for the prize might be less willing to share findings, enable material transfers, or cross-license key building blocks of knowledge, absent other incentives. If the lure of a prize impairs scientific exchange, then it may actually be counter-productive to the process of R&D innovation. Restructuring the prize, perhaps with intermediate milestones, can help mitigate this potential problem. Innovation inducement prizes, such as those offered by Innocentive, might tackle discrete milestones, such as upstream technical challenges. Providing an open source dividend that rewards sharing during the race for the prize is also another creative solution.¹¹⁹ By setting aside, say, 10 percent of the final prize for the best contributions to the final product receiving the prize, competing R&D groups might be motivated to cross-license IP and to share data on the way to the prize.

Prize remuneration requires specifying the outcomes sought and how the prize is distributed. Overspecifying the prize may curb interest among potential contenders or set aside promising, but unanticipated approaches. Underspecifying the prize risks wasting a reward on an outcome that does not address the real problem. A winner-takes-all prize rewards the first, but not necessarily the best, technology that surmounts the threshold. Providing prizes for second-comers can mitigate this problem. Staggering the payment over time allows the prize to be distributed for health outcomes realized, where documenting fewer deaths or DALYs is feasible.

Prizes give advantage to those already with the capital and resources to run the race. So if it matters that those in disease-endemic countries are full participants in the innovation process to develop treatments for themselves, then pull mechanisms alone fail to level the playing field for developing countries. Pull mechanisms, combined with push mechanisms targeted to R&D in disease-endemic countries, might help respond to this concern.

For all of their pluses and minuses, these various proposals enrich the public discourse over enhancing innovation and ensuring access. A hybrid approach to financing innovation for access might draw upon the strengths and lessen the shortcomings of both push and pull mechanisms. The empirical track record for these various proposed approaches to innovation is limited. So enabling the opportunity to pilot different approaches, including in combination, will be key. The optimal hybrid mix of approaches may differ by technology, by the market size, and by other factors.

For AIDS-related health technologies to be discovered, developed and delivered, incentives and fair returns to the public must be carefully balanced. To ensure improved health outcomes, these returns will take various forms: affordable access, innovation of novel technologies, and sustainability of supply. In turn, this paper suggests that certain mediating variables are key in delivering on these outcomes: transparency of the pharmaceutical R&D process and IP; conditions enabling open innovation; generic competition engaging multiple suppliers; and capacity building in disease-endemic countries to participate in the process of innovation. Factoring in these dimensions, an evaluative framework might hold whatever hybrid proposal comes forward to a set of accountable standards. Ensuring that public sector financing is strategically leveraged, with the sharing of knowledge and the fruits of research in mind, will be critical if the progress toward preventing and treating AIDS is to continue.

Part V. Conclusions

Meeting the twin challenges of innovation and access to health technologies is a cornerstone to combating HIV/AIDS, both to date and tomorrow. Scaling up treatment and sustaining the momentum of this work will require striking the right incentives, but also ensuring fair returns on the public investment in AIDS. This requires a close look at the dyadic and evolving relationship between intellectual property rights and innovation.

The TRIPS flexibilities affirmed by the Doha Declaration, particularly the possibility of using compulsory licensing, remain important instruments in negotiating for affordable treatment. Further challenges ahead should be expected, especially as developing countries are being asked to provide for IP protections well beyond the TRIPS requirements, in bilateral and other free trade agreements. Patent transparency and the availability of patent data not only are crucial for the exercise of TRIPS flexibilities, but also enable effective procurement and generic competition. As future treatment options entail the use of biologics and an effective vaccine is developed, the lengthier data exclusivity periods for biologics also pose greater challenges for innovation and access.

Meeting the needs of those living with HIV, especially in developing countries, will require more than a patent-driven system of pharmaceutical innovation. Patients must count where markets don't pay. In priming the pipeline for new

119 Love, James, Hubbard, Tim. Prizes for Innovation of New Medicines and Vaccines. *Ann Health Law* 2009; 18(2): 155-186.

and more effective AIDS treatments, the coming challenge will be to develop improved first-line regimens, second- and third-line treatments to respond to growing drug resistance and adverse side effects, to tailor combinations that meet the needs of children, and to adapt formulations to reach those in need where there is no cold chain. Diagnostics will have to come, part and parcel, with drugs, so that monitoring follows diagnosis as surely as treatment.

The public sector must strategically apply the use of IPRs to enhance innovation and safeguard affordable access to those health technologies that will become the future mainstay of preventing and treating AIDS. Alternatively, it can and should devise and test alternative incentive systems that de-link the market for innovations (and its incentives) from the market for production and access, which should incentivize robust generic competition. Such an enabling environment for innovation and access involves understanding where in the value chain of pharmaceutical R&D to intervene, whether to make supply-side or demand-side interventions, and where pooling and tiering might enable innovation or access.

Tiering can enable access for a segment of the market. Applied upstream in the R&D pipeline, the use of research tools, reagents and compounds critical to developing tomorrow's AIDS therapy might contribute to products eventually commercialized in low- and middle-income countries. Applied downstream in the delivery system, tiering carries the promise of more affordable access to end-products. Applied to the supply side, regulatory authorities can provide needed reassurances to procurement agencies of AIDS-related drugs and diagnostics. Applied to the demand side, a dual market allows for differential pricing. The challenge will be over where to draw the line between those receiving preferential treatment and those who will not. Most of the world's poor reside today in middle-income countries—their lot cast with the rising middle class of emerging economies, but perhaps their health circumstances more in common with low-income countries.

Pooling can lower the transaction costs to bring components of a vaccine together or drugs into a fixed-dose combination. IAVI's HIV Neutralizing Antibody Consortium applies pooling upstream while the Medicines Patent Pool will pool HIV drugs for combination therapy downstream. Pooling must move from case-by-case negotiation to a more collective setting of norms for sharing. Used in combination with tiering, pooling might enable access for developing countries to what otherwise might be proprietary. Used in open source innovation, pooling might yet change the scientific exchange norms if the fledgling, but exciting efforts of the Indian Council on Scientific and Industrial Research's Open Source Drug Discovery Initiative succeeds in bringing TB drugs from lead, to clinical trials and eventually to market.